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PD-44: mRNA signatures measured prior to H56:IC31 vaccination predict TB relapse in HIV negative adults successfully treated for drug-susceptible pulmonary TB

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Introduction: TB patients who are microbiologically cured on treatment completion remain at risk for relapse. We assessed performance of blood mRNA signatures for predicting TB relapse.

Methods: Adult drug-susceptible pulmonary TB patients were enrolled into a Prevention of Recurrence vaccine trial in South Africa and Tanzania (NCT03512249). Eligible participants tested Mtb sputum smear negative between weeks 22–26 of standard first-line TB treatment and were randomized (1:1) prior to treatment completion to receive two doses of H56:IC31 or placebo 56 days apart. Sputum microbiological investigations for TB recurrence were symptom-triggered for one year after second vaccination, and performed for all participants at end of follow-up. We analysed all culture-confirmed TB recurrences (relapse or reinfection) 14 days after second vaccination and randomly selected controls (1:2) with recurrence-free cure. Relapse was classified by a difference in ≤ 5 SNPs versus culture at enrolment. Twenty-three validated TB mRNA signatures were measured by microfluidic RT-qPCR on PAXgene whole blood collected in the final month of treatment prior to first vaccination.

Results: Thirty-seven participants with recurrence (18 relapse; 15 reinfection; 4 unknown) and 74 recurrence-free controls were included. Multiple signatures predicted TB relapse, but none predicted reinfection. The Xpert Host-Response signature performed best to predict TB relapse (AUC 0.81, 95%CI 0.72–0.91; p<0.0001). Signature scores and predictive performance did not differ between H56:IC31 or placebo recipients (Fig 1).

Conclusions: TB patients who relapsed had higher mRNA signature scores, synonymous with persistent systemic inflammation, in the final month of treatment. This suggests unsuccessful pathogen clearance and/or ongoing immune activation. Study arms appear comparable in risk of relapse prior to vaccination. mRNA signatures could be used to identify and monitor individuals at greatest risk of relapse.

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Conflicts of Interest
TJS is co-inventor of two mRNA signatures assessed in this work.

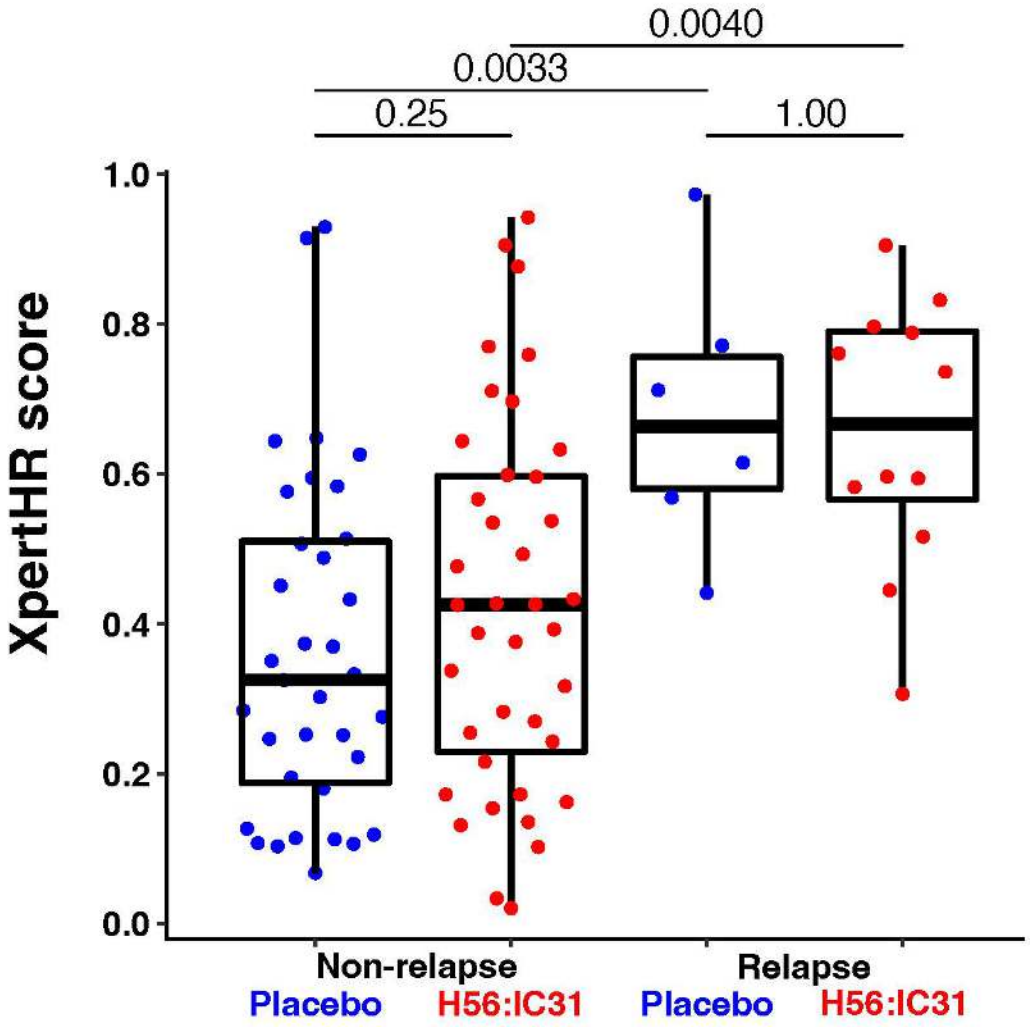

Figure 1. The Xpert Host-Response (HR) signature score measured in the final month of TB treatment, prior to vaccination, in H56:IC31 and placebo study arms, stratified by non-relapse and relapse through 1 year of follow-up from 14 days post second vaccination.